EUFEPS Conference
Membrane Drug Transporters: Impact on Drug Discovery, Development, Regulation and Usuage
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FDA Perspectives on Drug Transporters and Their Role in Drug Interactions

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Discussions on Drug Interactions

- **Publications of in vitro and in vivo drug interaction guidance documents**
  - *http://www.fda.gov/cder/guidance/clin3.pdf (1997)*
  - *http://www.fda.gov/cder/guidance/2635fnl.pdf (1999)*
- **Workshops/CDER rounds/Literature**
- **Advisory Committee meetings**
  - *April 20-21, 2003 (CYP3A inhibitor classification and P-gp inhibition)*
  - *November 17-18, 2003 (CYP2B6 and CYP2C8- related interactions)*
  - *November 3, 2004 (relevant principles of drug interactions)*
- **Launching of the FDA Drug Development and Drug Interaction website**
  - http://www.fda.gov/Cder/drug/drugInteractions/default.htm, May 2006

Concept paper published - Oct 2004

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Guidance for Industry: Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling

Draft published for public comment September 11, 2006
http://www.fda.gov/cder/guidance/6695dft.pdf

⟶ **Further discussion at an Advisory committee meeting, October 18, 2006, Rockville, MD**

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Key messages:

1. **Metabolism, transport, drug-interaction info key to benefit/risk assessment**
2. **Integrated approach (in vitro and in vivo) may reduce number of unnecessary studies and optimize knowledge**
3. **Study design/data analysis key to important information for proper labeling**

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Key messages:

4. **Clinical significance of a PK-based interaction needs to be interpreted based on exposure-response data/analyses**
5. **Classification of CYP inhibitors and substrates can aid in study design and labeling**
6. **Labeling language needs to be useful and consistent (new labeling rule, June 2006)**

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1. recommends CYP2C8, along with CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A, in the routine assessment of metabolic interactions (inhibition, induction and metabolic profiling)

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What's New?

2. When evaluating CYP inhibition in vitro

- I/Ki greater than 0.1 would indicate further in vivo study

- recommends the use of 2 CYP3A substrates

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What's New?

3. CYP induction can be addressed in vitro

- starting with CYP1A2 and CYP3A (assumption: co-induction of CYP3A and CYP2C/2B)

- induction of greater than 40% of the positive control would indicate further in vivo study

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What's New?

4. includes tables of recommended CYP probe substrates, inhibitors, inducers for in vitro and in vivo evaluation (these tables are posted on the FDA Drug Interaction website- easier future updates)

- suggests evaluation of PM vs EM in lieu of inhibition studies (CYP2D6, 2C9, 2C19) in vivo

- suggests evaluation of smokers vs non-smokers in lieu of induction studies (CYP1A2) in vivo

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What's New?

5. Recommends classification of CYP inhibitors (all 6 CYPs)

- strong, moderate, weak inhibitors (including grapefruit juice)

6. Defines sensitive substrates and substrates with NTR (for all 6 CYPs)

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What's New?

7. Briefly discusses

- protocol restrictions: use of dietary supplements, juices

- when the evaluation of multiple inhibitors may be appropriate

- use of cocktails for in vivo evaluation

- labeling including St John's wort

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What's New?

8. Provides a table of human transporters

9. Discusses in detail P-gp in vitro evaluation (substrate, inhibitor)

- Provides 2 decision trees

10. Briefly discusses other transporters (OATP, BCRP, MRP2, OATs, OCTs)

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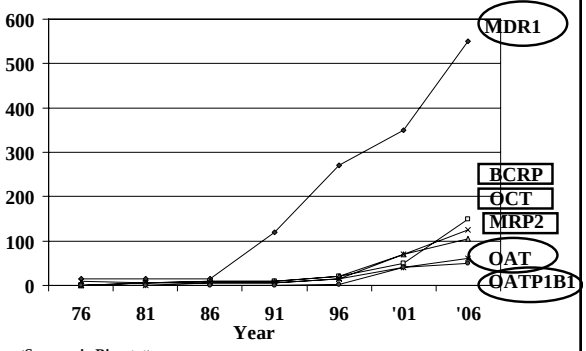
Number of published papers/patents



<Survey via Biovstat>

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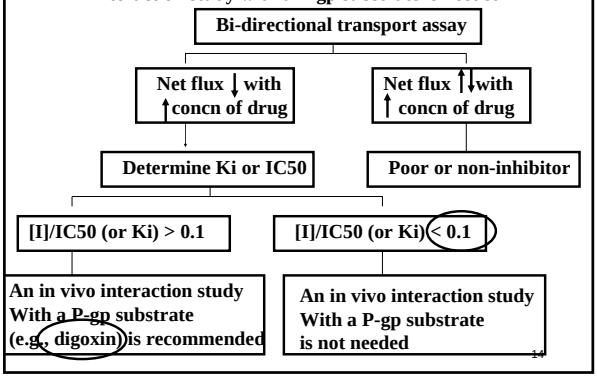
Figure 1. Decision tree to determine whether an investigational drug is an inhibitor for P-gp and whether an in vivo drug interaction study with a P-gp substrate is needed



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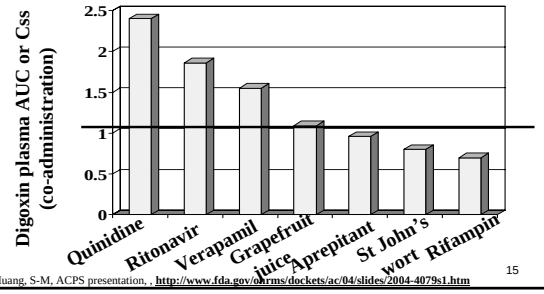
If a NME is an *inhibitor* of P-gp <u>in vitro</u>, <u>in vivo</u> study using digoxin may be appropriate



Huang, S-M, ACPS presentation, , http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4079s1.htm

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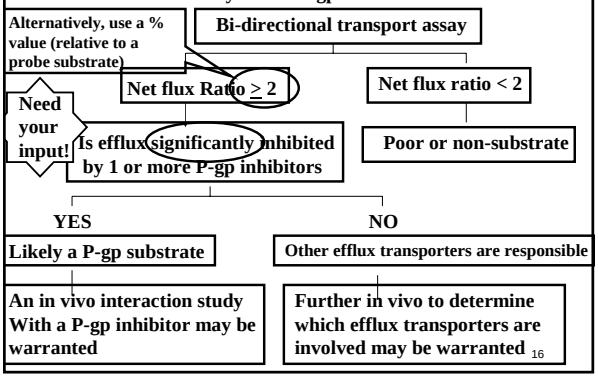
Figure 2. Decision tree to determine whether an investigational drug is a *substrate* for P-gp and whether an in vivo drug interaction study with a P-gp inhibitor is needed



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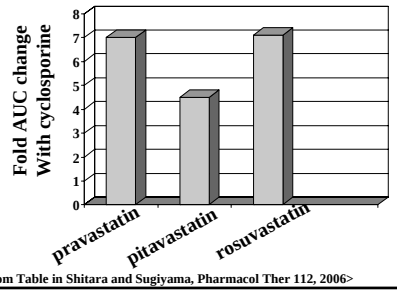
If a NME is a *substrate* for <u>P-gp in vitro:</u> an <u>in vivo</u> study with a P-gp- inhibitor (e.g., ritonavir, cyclosporine, verapamil) may be appropriate

[Cyclosporine affects multiple transporters, including OATP1B1]



<Data from Table in Shitara and Sugiyama, Pharmacol Ther 112, 2006>

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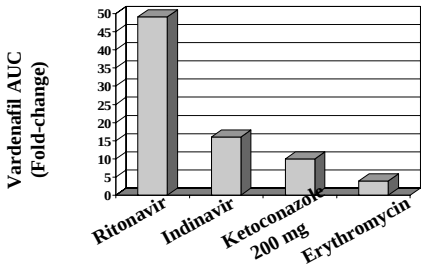
If a NME is a *substrate* for <u>P-gp and CYP3A</u> -> a clinical study with a strong inbitors for both (e.g., ritonavir) may be appropriate

***[Ritonavir affects multiple pathways*]**



Huang, S-M, ACPS presentation, , http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4079s1.htm

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How do we label transporter-based interactions?

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"Class" labeling of drugs that are substrates of CYP3A
[proposed in the 2006 draft guidance on "drug interactions"]

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Labeling

If a drug has been determined to be a sensitive CYP3A *substrate* or a CYP3A *substrate* with a narrow therapeutic range, it does not need to be tested with all strong or moderate inhibitors of CYP3A to warn about an interaction with "strong" or "moderate" CYP3A inhibitors

FDA Advisory Committee for pharmaceutical sciences and Clinical Pharmacology Subcommittee meeting. Issues drug interaction concept paper. Rockville, MD. November 3, 2004; http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4079b1.htm; http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4079s1.htm; Huang, S-M, presentation

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Examples of strong and moderate CYP3A inhibitors

Strong CYP3A inhibitors	*Moderate CYP3A inhibitors*
atanazavir clarithromycin indinavir itraconazole ketoconazole nefazodone nelfinavir ritonavir saquinavir telithromycin	amprenavir aprepitant diltiazem erythromycin fluconazole fosaprenavir *grapefruit juice(a)* verapamil *Weak CYP3A inhibitors* cimetidine

A "strong inhibitor" is one that caused a ≥ 5-fold increase in the plasma AUC values of CYP3A substrates (not limited to midazolam) in clinical evaluations

A "moderate inhibitor" is one that caused a ≥ 2- but < 5-fold increase in the AUC values of sensitive CYP3A substrates when the inhibitor was given at the highest approved dose and the shortest dosing interval in clinical evaluations

(a) The effect varies widely

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Labeling example - CYP3A substrate

Eletriptan	AUC	Cmax
Ketoconazole	8x	4x

Should not be used within at least 72 hours **with strong CYP3A inhibitors…. Ketoconazole, itraconazole, ritonavir, nelfinavir, nefazodone, clarithromycin.**

Not studied

<(Relpax (eletriptan) PDR labeling May 2005>

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Do we have sufficient data for "class" labeling of drugs that are substrates of transporters?

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"Class" labeling of drugs that are inhibitors of CYP3A
[proposed in the 2006 draft guidance on "drug interactions"]

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Labeling

If a drug has been determined to be a strong *inhibitor* of CYP3A, it does not need to be tested with all CYP3A substrates to warn about an interaction with "sensitive CYP3A substrates" and "CYP3A substrates with narrow therapeutic range".

FDA Advisory Committee for pharmaceutical sciences and Clinical Pharmacology Subcommittee meeting. Issues drug interaction concept paper. Rockville, MD. November 3, 2004; http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4079b1.htm; http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4079s1.htm; Huang, S-M, presentation

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Examples of sensitive CYP3A substrates or CYP3A substrates with NTR

Sensitive CYP3A substrates	CYP3A Substrates with Narrow therapeutic range
budesonide, buspirone, eplerenone, eletriptan, felodipine, lovastatin, midazolam, saquinavir, sildenafil, simvastatin, triazolam, vardenafil	Alfentanil, astemizole(a), cisapride(a), cyclosporine, diergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine(a)

"sensitive CYP3A substrates" refer to drugs whose plasma AUC values are increased 5-fold or more when co-administered with CYP3A inhibitors
"CYP3A substrates with narrow therapeutic range" refer to drugs whose exposure-response data are such that increases in their exposure levels by the concomitant use of CYP3A inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes);
(a) not available in US

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Labeling example- CYP3A inhibitor

Telithromycin	AUC
Midazolam	6x

- Telithromycin is a strong inhibitor of the cytochrome P450 3A4 system
- Use of simvastatin, lovastatin, or atorvastatin concomitantly with KETEK should be avoided
- The use of KETEK is contraindicated with cisapride, pimozide

Not studied

<Pysicians' Desk Reference at http://pdrel.thomsonhc.com/pdrel/librarian >

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Do we have sufficient data for "class" labeling of drugs that are inhibitors of transporters?

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Labeling examples

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Fexofenadine

These studies indicate that ketoconazole or erythromycin co-administration *enhances* fexofenadine gastrointestinal absorption. This observed increase in the bioavailability of fexofenadine may be due to *transport-related effects, such as p-glycoprotein*. *In vivo* animal studies also suggest that in addition to enhancing absorption, ketoconazole decreases fexofenadine gastrointestinal secretion, while erythromycin may also decrease biliary excretion.

http://www.fda.gov/cder/foi/label/2004/21704lbl.pdf 31

Fexofenadine (2)

Interactions with Fruit Juices

Fruit juices such as grapefruit, orange and apple may *reduce* the bioavailability and exposure of fexofenadine. This is based on the results from 3 clinical studies using histamine induced skin wheals and flares coupled with population pharmacokinetic analysis. …… Therefore, to maximize the effects of fexofenadine, it is recommended that ALLEGRA-D 24 HOUR *should be taken with water*

http://www.fda.gov/cder/foi/label/2004/21704lbl.pdf 32

Eplerenone

Eplerenone is not a substrate or an inhibitor of *P-glycoprotein* at clinically relevant doses

No clinically significant drug-drug pharmacokinetic interactions were observed when eplerenone was administered with *digoxin*

http://www.fda.gov/cder/foi/label/2003/21437se1-002_inspra_lbl.pdff 33

Pramipexole

Cimetidine: **Cimetidine, a known inhibitor of renal tubular secretion of organic bases via the cationic transport system, caused a 50% increase in pramipexole AUC and a 40% increase in half-life (N=12).**

Probenecid: **Probenecid, a known inhibitor of renal tubular secretion of organic acids via *the anionic transporter*, did not noticeably influence pramipexole pharmacokinetics (N=12).**

http://pdrel.thomsonhc.com/pdrel/librarian/PFDefaultActionId/pdrcommon.IndexSearchTranslator#PDRP RE01el/2004/21704lbl.pdf 34

Pramipexole (cont'd)

***Other drugs eliminated via renal secretion:* : Population pharmacokinetic analysis suggests that coadministration of drugs that are secreted by the cationic transport system (e.g., cimetidine, ranitidine, diltiazem, triamterene, verapamil, quinidine, and quinine) decreases the oral clearance of pramipexole by about 20%, while those secreted by the anionic transport system (e.g., cephalosporins, penicillins, indomethacin, hydrochlorothiazide, and chlorpropamide) are likely to have little effect on the oral clearance…**

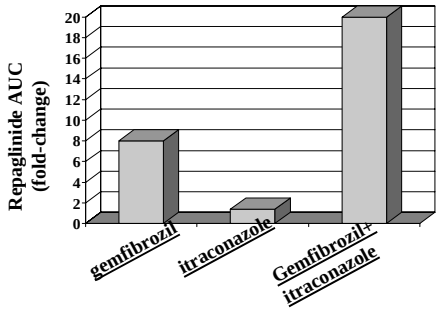
http://pdrel.thomsonhc.com/pdrel/librarian/PFDefaultActionId/pdrcommon.IndexSearchTranslator#PDRP RE01el/2004/21704lbl.pdf 35

Dofetilide

Dofetilide is eliminated in the kidney by cationic secretion. Inhibitors of *renal cationic secretion* are contraindicated with TIKOSYN. In addition, drugs that are actively secreted via this route (e.g., triamterene, metformin and amiloride) should be co-administered with care as they might increase dofetilide levels.

http://pdrel.thomsonhc.com/pdrel/librarian/PFDefaultActionId/pdrcommon.IndexSearchTranslator#PDRDIA01 36

Combination of CYP and transporter interactions



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Repaglinide

Caution should be used in patients already on PRANDIN and gemfibrozil - blood glucose levels should be monitored and PRANDIN dose adjustment may be needed. Rare postmarketing events of serious hypoglycemia have been reported in patients taking PRANDIN and gemfibrozil together. Gemfibrozil and itraconazole had a synergistic metabolic inhibitory effect on PRANDIN. Therefore, patients taking PRANDIN and gemfibrozil should not take itraconazole.

PDR on Orandin, December 2004

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Summary

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P-gp- based interactions

- **Most well developed**
- **Information increasingly included in labeling**
- **To determine when to evaluate in vivo: need agreed-upon criteria to evaluate in vitro (preclinical) data- presented in the September 2006 draft guidance**
- **Digoxin a clinically relevant substrate**
- **proposed general transporter inhibitors**

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Other transporter- based interactions

- **In vitro methodologies being developed**
- **Some information has been included in labeling**
- **Need continued research; need probe substrates/inhibitors**
- **Short-term recommendations may be drug- or "therapeutic class-" specific**

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References

- **Lei Zhang, John M. Strong, Wei Qiu, Lawrence J. Lesko, and Shiew-Mei Huang. Scientific Perspectives on Drug Transporters and Their Role in Drug Interactions [PDF] [external link] *Mol Pharm.* 2006; 3(1), 62-69, Epub Jan 4 2006.**
- **Guidance for industry: Drug Interaction Studies: Study design, Data analysis and Implications for Dosing and Labeling (Issued for public comment, September 11, 2006, http://www.fda.gov/cder/guidance/6695dft.pdf).**
- **FDA Drug Development and Drug Interactions Website; http://www.fda.gov/Cder/drug/drugInteractions/default.htm, established May 2006**

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Drug Interactions working group

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Questions?

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